

## CORRESPONDENCE

### Research Correspondence

# Pre-Hospital Reduced-Dose Fibrinolysis Coupled With Urgent Percutaneous Coronary Intervention Reduces Time to Reperfusion and Improves Angiographic Perfusion Score Compared With Prehospital Fibrinolysis Alone or Primary Percutaneous Coronary Intervention

## Results of the PATCAR Pilot Trial

**To the Editor:** In over 27,000 patients treated for ST-segment elevation myocardial infarction (STEMI) with primary percutaneous coronary intervention (PCI) in the U.S., the average time from symptom onset to PCI (ischemic time) was 5.5 h (1), which is well beyond the 2-h goal for optimal salvage (2). Brodie et al. (3) showed that ischemic times  $\leq 2$  h decreased mortality compared with longer ischemic times (4.3% vs. 9%,  $p = 0.04$ ). The PATCAR (Prehospital Administration of Thrombolytic Therapy with Urgent Culprit Artery Revascularization) pilot trial evaluated the feasibility that reduced-dose pre-hospital fibrinolysis coupled with urgent PCI could reduce ischemic time in STEMI patients.

Four STEMI patient groups were evaluated: Group A, full-dose, pre-hospital fibrinolysis followed by treatment in the coronary care unit; Group B, one-half-dose pre-hospital reteplase followed by urgent PCI; Group C, patients who were fibrinolytic ineligible, and Group D, patients not transported by participating emergency medical systems (EMS) units. Groups C and D were treated with primary PCI at the STEMI center.

Reperfusion:  $\geq 70\%$  ST-segment resolution on 12-lead electrocardiogram with reduction in chest pain or Thrombolysis In Myocardial Infarction (TIMI) flow grade 2 to 3 infarct-related artery (IRA) flow on initial or post-PCI angiogram.

Major bleeding (GUSTO [Global Use of Strategies to Open Occluded Arteries] definition): Bleeding resulting in substantial hemodynamic instability requiring intervention.

Differences among the treatment groups were assessed by the Fisher exact test for categorical variables and by analysis of variance for continuous variables with normal distribution. Otherwise, analysis of variance on ranks was used. Pair-wise multiple comparisons were done using the Dunn method. A 2-tailed  $p$ -value  $< 0.05$  was considered statistically significant.

Informed consent was obtained from 73 patients enrolled from September 2003 to January 2006. Of 60 STEMI patients identified before entering the hospital, 46 were fibrinolytic eligible and were treated in the ambulance with 10 units reteplase, intravenous heparin and oral aspirin, and randomized to either a second 10-unit dose of reteplase (Group A,  $n = 22$ ) or urgent catheterization with PCI (Group B,  $n = 24$ ). Fibrinolytic-ineligible patients and patients brought in by nonparticipating EMS systems treated with primary PCI alone were prospectively analyzed for comparison (Group C+D-non-transfer [NT],  $n = 27$ ). Four patients were excluded from analysis in Groups A and B because of

inadvertent treatment delays or false-positive electrocardiogram results.

Group B experienced shorter ischemic times than Group A, ( $165 \pm 54$  min vs.  $270 \pm 109$  min,  $p < 0.05$ ) and Group C+D-NT ( $221 \pm 143$  min, trend,  $p = 0.08$ ) (Table 1). The time from contact to reperfusion was  $114 \pm 33$  min in Group B, compared with  $168 \pm 59$  min in Group A and  $148 \pm 94$  min in Group C+D-NT ( $p = 0.014$ , B vs. A and  $p = 0.044$  for all 3 groups).

Eighty-two percent of Group B patients had TIMI flow grade 2 or 3 in the IRA on initial angiography, compared with 37% of primary PCI patients ( $p = 0.002$ ) (Table 1). The incidence of angiographic perfusion score  $\geq 10$  (4) in Group B patients was 67%, compared with 22% in Group C+D-NT ( $p = 0.003$ ) (Table 1, Fig. 1).

No patient experienced an intracranial hemorrhage, and strokes were rare. One patient in Group B experienced a major bleed that occurred 4 days after admission and was not secondary to fibrinolytic therapy (Table 1).

Initial IRA TIMI flow grades of 2 to 3 are correlated with improved survival (5) and were observed in 82% of Group B patients, compared with only 37% in Group C+D-NT ( $p = 0.002$ ). Full reperfusion (TIMI angiographic perfusion score  $\geq 10$ ) is also correlated with survival (4), and was found in 67% of Group B compared with 22% of Group C+D-NT ( $p = 0.003$ ) patients.

LeMay et al. (6) reported that full-dose tenecteplase-coupled angioplasty was not associated with increased bleeding risk. Bleeding risk was not increased with partial-fibrinolysis-coupled PCI in our patients.

Sixty-eight percent of patients crossed over from Group A to rescue PCI for persistent symptoms, ST-segment elevation, or hemodynamic instability. Less than 50% of these had TIMI flow grade 2 or 3 IRA compared with 80% of the patients in Group B. This suggests that routine PCI immediately after pre-hospital fibrinolysis, irrespective of clinical setting, should be the standard of care.

The majority of ASSENT (Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Interventions)-4 PCI patients had significant delays from onset of pain to treatment; those who received fibrinolytic agents in the ambulance had more favorable outcomes than those treated with

**Table 1** Comparison of Timing of Events in Each Group

	Groups			ANOVA
	A	B	C+D-NT	
Number of patients	20	22	27	
Onset to contact (min)	102 ± 98 (n = 20)*	50 ± 44 (n = 22)	58 ± 55 (n = 23)	p = 0.03
Onset to door (min)	166 ± 118 (n = 20)	107 ± 46 (n = 22)	115 ± 90 (n = 25)	NS
Onset to lytic (min)	144 ± 108 (n = 20)	91 ± 45 (n = 22)	NA	N/A
Ischemic time (min)	270 ± 109 (n = 20)*	165 ± 54 (n = 22)†	221 ± 143 (n = 24)	p = 0.002
Contact to reperfusion (min)	168 ± 59 (n = 20)	114 ± 33 (n = 22)‡	148 ± 94 (n = 23)	p = 0.044
Onset to balloon (min)	N/A	180 ± 53 (n = 18)	225 ± 134 (n = 22)	N/A
Door to balloon (min)	N/A	74 ± 30 (n = 18)§	136 ± 88 (n = 23)	N/A
Revascularization within 48 h of admittance	85%	82%	85%	NS
TIMI flow grade 2 to 3 on initial angiograph	60% (n = 20)	82% (n = 22)	37% (n = 27)	p = 0.007
TIMI perfusion score ≥10	53% (n = 19)	67% (n = 18)¶	22% (n = 23)	p = 0.013
>70% ST-segment resolution by CCU	70% (n = 20)	68% (n = 22)	63% (n = 24)	NS
GUSTO major bleeding#	0% (n = 20)	4.5% (n = 22)	0% (n = 27)	NS
ICH	0% (n = 20)	0% (n = 22)	0% (n = 27)	NS
Any stroke	0% (n = 20)	0% (n = 22)	3.7% (n = 27)	NS
Reinfarction	0% (n = 19)	0% (n = 21)	0% (n = 26)	NS
30-day mortality	0% (n = 19)	4.8% (n = 21)	3.8% (n = 26)	NS

\*p < 0.05 Group A versus Group B. †p = 0.08 Group B versus Group C+D-NT. ‡p < 0.014 Group A versus Group B. §p < 0.05 Group B versus Group C+D-NT. ||p = 0.003 Group B versus Group C+D-NT. ¶p = 0.002 Group B versus Group C+D-NT. #Circulation 1997;95:2508-16.

ANOVA = analysis of variance among 3 groups; CCU = coronary care unit; GUSTO = Global Use of Strategies to Open Occluded Arteries; ICH = intracranial hemorrhage; n = total data points available for analysis; N/A = not applicable; NS = not significant; TIMI = Thrombolysis In Myocardial Infarction.

primary PCI alone (7). The total stroke rate of 1.8% in the fibrinolytic arm of the ASSENT-4 study was similar to the stroke rate reported in the ASSENT-3 study with the same fibrinolytic agent (8).

This was a relatively small feasibility study that was not powered to detect a difference in major outcomes (mortality, stroke, reinfarction, and major bleeding) among the groups. Groups A and B were randomized; however, Group C+D-NT was an observational arm, which limits interpretation of the findings.

The strategy of diagnosing STEMI in chest pain patients and administering reduced-dose fibrinolytic agents, heparin, aspirin, and clopidogrel in the field with simultaneous notification of the

PCI team significantly reduced ischemic time, improved the quality of early myocardial reperfusion, and was not associated with excessive bleeding risks compared with full-dose pre-hospital fibrinolysis alone or primary PCI in an urban setting. Patients with brief pre-hospital cardiac arrest, those with shock, and elderly patients were not excluded, suggesting that this strategy might be broadly applicable. Our data and those of Thiele et al. (9) suggest that reduced-dose pre-hospital fibrinolysis allows safe transport of STEMI patients to PCI centers for urgent culprit artery PCI, and may be a superior approach compared with transporting patients to the closest non-PCI hospital for fibrinolytic therapy. Whether this strategy is superior to primary PCI remains to be determined. Further evaluation of the strategy of pre-hospital fibrinolysis acceleration of STEMI treatment coupled with urgent PCI (FAST-PCI) in a large multicenter randomized trial compared with primary PCI seems warranted.

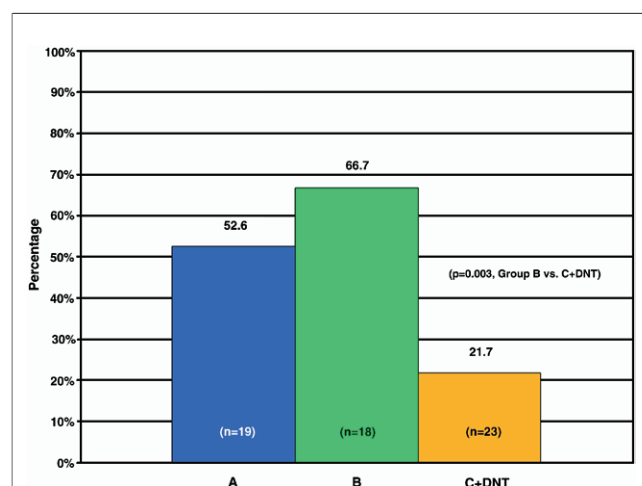
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**Figure 1** Percentage of Patients With Angiographic Perfusion Score ≥10

Percentage of patients with infarct-related artery angiographic Thrombolysis In Myocardial Infarction perfusion score ≥10 on final angiograph in Groups A, B, and C+D-NT.

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## REFERENCES

1. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA* 2000;283:2941-7.
2. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996;348:771-5.
3. Brodie BR, Stuckey TD, Wall TC, et al. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1998;32:1312-9.
4. Gibson CM, Murphy SA, Morrow DA, et al. Angiographic perfusion score: an angiographic variable that integrates both epicardial and tissue level perfusion before and after facilitated percutaneous coronary intervention in acute myocardial infarction. *Am Heart J* 2004;148:336-40.
5. Stone GW, Cox D, Garcia E, et al. Normal flow (TIMI-3) before mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction: analysis from the primary angioplasty in myocardial infarction trials. *Circulation* 2001;104:636-41.
6. Le May MR, Wells GA, Labinaz M, et al. Combined angioplasty and pharmacological intervention versus thrombolysis alone in acute myocardial infarction (CAPITAL AMI study). *J Am Coll Cardiol* 2005;46:417-24.
7. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006;367:569-78.
8. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 2001;358:605-13.
9. Thiele H, Scholz M, Engelman L, et al. ST-segment recovery and prognosis in patients with ST-elevation myocardial infarction reperfused by prehospital combination fibrinolysis, prehospital initiated facilitated percutaneous coronary intervention, or primary percutaneous coronary intervention. *Am J Cardiol* 2006;98:1132-9.

## Letters to the Editor

### Tissue Doppler Imaging: Diagnostic and Prognostic Value

The paper by Yu et al. (1) in the *Journal* summarized the applications of tissue Doppler imaging (TDI). However, we consider additional clinical applications to be very important. We have used TDI routinely for after-transplant monitoring since 1998. Our studies proved TDI's reliability for early detection of acute rejection and transplant coronary artery disease (TxCAD) and showed that serial TDI can spare patients unnecessary and distressing routine invasive examinations (2,3). Tissue Doppler imaging also appeared reliable for prognostic estimations after heart transplantation and for the evaluation of rejection severity and guidance of antirejection therapy (2,3). Recently we showed that TDI can also be helpful in evaluations of myocardial recovery during mechanical unloading after ventricular assist device (VAD) implantation (4).

We do not agree with Yu et al. (1) that myocardial deformation imaging is not ready for routine clinical use. Recently, Perk et al. (5) emphasized the clinical reliability of the method. We use 2-dimensional strain imaging routinely for patients' evaluation before and after coronary surgery and also for noninvasive monitoring of allograft function after heart transplantation. Additionally, 2-dimensional strain imaging is our method of choice for patient selection for surgical ventricular restoration (SVR) after severe myocardial infarction. We found that the systolic dyssynchrony indexes and global strain rate are reliable for evaluation of myocardial functional changes during postoperative reverse remodeling processes after SVR. The 2-dimensional strain method also improved our ability to evaluate cardiac recovery after VAD implantation and was decisive for the decision to wean 5 patients

from their assist devices. In heart-transplanted patients, we found that systolic strain dyssynchrony and dyssynchrony indexes are more useful than pulsed-wave TDI parameters for differentiation between angiographic TxCAD with and without proximal focal stenoses.

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## REFERENCES

1. Yu CM, Sanderson JE, Marwick HT, Oh KH. Tissue Doppler imaging—a new prognosticator for cardiovascular diseases. *J Am Coll Cardiol* 2007;49:1903-14.
2. Dandel M, Hummel M, Müller J, et al. Reliability of tissue Doppler wall motion monitoring after heart transplantation for replacement of invasive routine screenings by optimally timed cardiac biopsies and catheterizations. *Circulation* 2001;104 Suppl:1184-91.
3. Dandel M, Wellnhofer E, Hummel M, et al. Early detection of left ventricular dysfunction related to transplant coronary artery disease. *J Heart Lung Transplant* 2003;22:1353-64.
4. Dandel M, Weng Y, Siniawski H, et al. Long-term results in patients with idiopathic dilated cardiomyopathy after weaning from left ventricular assist devices. *Circulation* 2005;112:I-37-45.
5. Perk G, Tunick PA, Kronzon I. Non-Doppler two-dimensional strain imaging by echocardiography—from technical considerations to clinical applications. *J Am Soc Echocardiogr* 2007;20:234-43.